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# Safety and functional outcome of thrombolysis in dissection-related ischemic stroke: a meta-analysis of individual patient data

Zinkstok, S M ; Vergouwen, M D I ; Engelter, S T ; Lyrer, P A ; Bonati, L H ; Arnold, M ; Mattle, H P ; Fischer, U ; Sarikaya, H ; Baumgartner, R W ; Georgiadis, D ; Odier, C ; Michel, P ; Putaala, J ; Griebenow, M ; Wahlgren, N ; Ahmed, N ; van Geloven, N ; de Haan, R J ; Nederkoorn, P J

Abstract: BACKGROUND AND PURPOSE: The safety and efficacy of thrombolysis in cervical artery dissection (CAD) are controversial. The aim of this meta-analysis was to pool all individual patient data and provide a valid estimate of safety and outcome of thrombolysis in CAD. METHODS: We performed a systematic literature search on intravenous and intra-arterial thrombolysis in CAD. We calculated the rates of pooled symptomatic intracranial hemorrhage and mortality and indirectly compared them with matched controls from the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register. We applied multivariate regression models to identify predictors of excellent (modified Rankin Scale=0 to 1) and favorable (modified Rankin Scale=0 to 2) outcome. RESULTS: We obtained individual patient data of 180 patients from 14 retrospective series and 22 case reports. Patients were predominantly female (68%), with a mean±SD age of 46±11 years. Most patients presented with severe stroke (median National Institutes of Health Stroke Scale score=16). Treatment was intravenous thrombolysis in 67% and intra-arterial thrombolysis in 33%. Median follow-up was 3 months. The pooled symptomatic intracranial hemorrhage rate was 3.1% (95% CI, 1.3 to 7.2). Overall mortality was 8.1% (95% CI, 4.9 to 13.2), and 41.0% (95% CI, 31.4 to 51.4) had an excellent outcome. Stroke severity was a strong predictor of outcome. Overlapping confidence intervals of end points indicated no relevant differences with matched controls from the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register. CONCLUSIONS: Safety and outcome of thrombolysis in patients with CAD-related stroke appear similar to those for stroke from all causes. Based on our findings, thrombolysis should not be withheld in patients with CAD.

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# SAFETY AND FUNCTIONAL OUTCOME OF THROMBOLYSIS IN DISSECTION-RELATED ISCHEMIC STROKE: A META-ANALYSIS OF INDIVIDUAL PATIENT DATA.

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**Summary**

***Background*** - Ischemic stroke is often treated with thrombolysis in the acute phase, irrespective of the cause. It remains unclear whether thrombolysis is safe in patients with cervical artery dissection (CAD). The aim of the current meta-analysis is to pool all available series and individual patient data and to provide a valid estimate of safety and outcome of thrombolytic therapy in patients with CAD-related stroke.

***Methods*** - We performed a systemic literature search on thrombolytic treatment (intravenous thrombolysis only (IVT), intra-arterial thrombolysis only (IAT), or combined procedures) in patients with CAD-related stroke. Individual patient data (IPD) were collected from manuscripts or by contacting the authors. Pooled symptomatic intracerebral hemorrhage (SICH) and mortality rates, only corrected for heterogeneity were calculated. In a multivariate regression model, with functional outcome on the modified Rankin Scale (mRS) as the dependent variable, adjustments were made for the following possible explanatory variables: gender, age, preceding trauma, dissected artery, onset to treatment time, stroke severity on the National Institutes of Health Stroke Scale score (NIHSS), and treatment (IVT, IAT or combined).

***Findings*** - Fourteen retrospective series and 22 case reports comprising 190 patients were identified. From 180 patients IPD were available. Patients were predominantly (68%) female with a median age of 46 years. Patients presented with severe stroke symptoms (median NIHSS score 16 points). Treatment modality was IVT in 68%, IAT in 20%, and combined in 12%. The pooled SICH rate was 3.1% (95% CI 1.3-7.2%). Overall mortality was 8.1% (95% CI 4.9-13.2%). 37% (95% CI 29-49%) reached excellent outcome (mRS 0-1). Stroke severity on NIHSS before treatment was the only predictor for functional outcome.

***Interpretation*** - The results of our study suggest that thrombolysis in patients with CAD-related stroke is safe. There is no evidence to exclude patients suspected of dissection-related stroke from thrombolytic treatment.

## Introduction

Approximately 2% of all ischemic strokes are caused by cervical artery dissection (CAD), whereas in patients under 50, this number is 10-25%.[1;2] CAD is characterized by the presence of an intramural hematoma due to an intimal tear in the carotid or vertebral artery. Subsequent brain ischemia is believed to be thrombo-embolic rather than hemodynamic.[3] Randomised trials investigating thrombolytic therapy in acute ischemic stroke patients did not exclude patients with CAD.[4-10] However, safety and efficacy has never been investigated in this particular subgroup. Therefore, it remains unknown if thrombolytic therapy can be given in ischemic strokes secondary to CAD.

The most feared complication in thrombolytic therapy in stroke is symptomatic intracranial hemorrhage (SICH). In the subgroup of CAD patients, who suffer from a damaged vessel wall, this small but non-negligible risk may potentially be higher. Besides intracerebral hemorrhage, other potential complications of thrombolytic therapy in this group of patients are pseudo-aneurysm formation and subarachnoid bleeding of an intracranially extending dissection. Nevertheless, several retrospective case series suggested that thrombolytic therapy in CAD patients is safe.[11;12] The aim of the current meta-analysis is to pool all available series and individual patient data and to provide a valid estimate of safety and outcome of thrombolytic therapy in patients with CAD-related stroke. In addition, predictors of outcome after thrombolytic treatment in CAD-patients will be evaluated.

## Methods

*Study selection*

We systematically searched the PUBMED and EMBASE database up to 2010 (week 11) for publications on thrombolytic treatment in patients with CAD-related ischemic stroke, using the following combination of variables: ["dissection"] AND ["carotid" or "vertebral" or "cervical" or "extracranial" or "stroke" or "brain ischemia" or "brain infarction"] AND ["thrombolysis" or "recombinant tissue plasminogen activator" or "rtPA" or "tissue plasminogen activator" or "tPA" or "urokinase" or "pro-urokinase"]. Furthermore, we searched for relevant studies in the Cochrane Library and Cochrane Central Register of Controlled Trials, and hand searched citations of the retrieved studies. Finally, experts in the field were consulted.

We included studies that investigated thrombolytic therapy in patients with CAD-related stroke, either when this was analyzed as a main analysis or as a subgroup analysis. Since the number of publications on this topic is scarce, no lower limit of number of patients per study was applied. For the same reason, we included English, German and French publications and publications in other languages as long as an abstract in English, German of French was provided. Patients with a dissection limited to the intracranial vessel(s) only, or an aortic dissection with extension into the cervical arteries, were excluded, because of the different pathogenesis involved.[13] CAD could be diagnosed with combined color duplex or sonography, CTA, MRA, or conventional angiography. Diagnosis of a dissection could be confirmed before or after thrombolytic therapy. Since most of the included studies did not systematically assess the degree of stenosis before and after treatment, recanalization could not be included as a reliable variable in our analysis. We analyzed the following treatment categories: intravenous thrombolysis only (IVT), intra-arterial thrombolysis only (IAT), and combined treatment. Combination treatment was defined as IVT and/or IAT, followed by either mechanical thrombectomy, stent placement or other endovascular procedures. Crucial for the aim of the present study is that thrombolytic therapy had to be administered in the

acute phase of ischemic stroke, ultimately within 24 hours after symptom onset. Studies describing interventions started beyond 24 hours, often because of secondary worsening of a patient, are not in the domain of the present study.

*Data extraction*

The following baseline characteristics were collected: gender, age, preceding trauma (including minor trauma), stroke severity at presentation in terms of the National Institutes of Health Stroke Scale score (NIHSS), dissected artery (carotid or vertebral artery), vessel occlusion before treatment, intracranial extension, time from symptom onset to treatment, treatment modality (IVT only, IAT only or combined) and duration of follow-up.

Regarding safety, the following variables were extracted: mortality, symptomatic intracerebral hemorrhage (SICH) as defined by the authors, and recurrent stroke. Additional adverse events as reported by the authors, were collected and described. Functional outcome was assessed by means of the level of dependency at follow-up. Excellent outcome was defined as 0-1 on the modified Rankin Scale (mRS), and favourable outcome as a mRS score of 0-2.

Data extraction was performed by two independent observers (SZ, PN), and disagreements were resolved by consensus. When mRS was unavailable, two independent observers reconstructed the score but only if this could clearly be deducted from the case description, according to the official mRS criteria.[14] Adverse events were reported as defined by the investigators of the individual studies.

*Individual patient data (IPD)*

Of all case series that reported summarised data only, the authors were contacted, and we allowed them to provide individual patient data (IPD) of both published and unpublished cases. We sent them a uniform and pre-specified datasheet, allowing them to fill out IPD

electronically. Authors of case report were contacted if data we needed for the analysis were missing in the manuscript.

*Statistical analyses*

All analyses were performed on level of individual patient data with pooled proportion mixed analyses. Pooled proportions for the primary safety endpoints SICH and death rate, and for excellent or favourable outcome, were calculated accounting for heterogeneity of the studies. Since intravenous thrombolysis is of particular interest of this meta-analysis proportions were also calculated for patients treated with IVT only. The following variables were included in two univariate models as predictors for excellent and favourable outcome respectively: gender, age, preceding trauma, dissected artery, onset to treatment time, stroke severity (NIHSS) and treatment modality. Onset to treatment time was analyzed both as continuous and as categorical variable (< 120 minutes, 120-180 minutes and > 180 minutes). In a subsequent multivariate analysis, adjustments were made for the predictors that were significantly ($p < 0.05$) associated with both excellent and favourable outcome in the univariate analysis.

*Publication bias*

A sensitivity analysis was performed with extraction of the results of the case reports, to evaluate the effect of possible publication bias in the latter.

## Findings

*Studies*

Our search strategy yielded 186 citations. After evaluating the abstracts and, if needed, full texts, 150 publications were excluded. As a result, 36 publications were available for this meta-analysis, including 190 patients. All studies were retrospective series or single case reports; no randomized controlled clinical trials were identified. In total, 14 case series presented data of thrombolysis in dissection related stroke, including 166 patients.[11;12;15-26] Nine studies used data from stroke registers [15;19;23;26] or thrombolysis registers [11;16;21;27] and one was based on a non-defined hospital registry.[20] Of these, 3 studies were multicenter studies.[11;15;27] An overview of the study characteristics of the case series is presented in Table 1. In addition, 22 case reports were retrieved describing another 24 patients.[28-49]. IPD were (partly) available in 33 publications including 72 patients. From the remaining 3 publications presenting aggregate data only, IPD of another 108 patients could be collected of which some had not been published yet. In total, individual patient data from 180 patients were available for this study.

*Baseline characteristics*

Patients of which IPD were available (n=180) were predominantly female (68%) with a mean age of 46 ± 11 years. Most patients (60%) presented with severe stroke symptoms (NIHSS ≥ 15). Median onset to treatment time was 165 minutes, whereas 6% of the IVT treated patients was treated beyond the therapeutic window of 4.5 hours after symptom onset. All baseline characteristics are presented in Table 2.

*Safety*

The pooled mortality rate was 8.1% (95% CI 4.9%-13.2%). However, in 7 patients (4%) survival or death was not specified. Pooled mortality in patients treated with IVT only was 6.7% (95% CI 3.4-12.8%). SICH occurred in 8 of 180 patients (3.1%; 95% CI 1.3-7.2%), of

which 2 were fatal. In IVT only group, 4 patients experienced SICH (3.3%; 95% CI 1.2-8.5%). Recurrent stroke occurred in 4.5% (95% CI 2.3-8.7%) and in 6.8% (95% CI 3.4-13.0%) in patients treated with IVT only.

In addition, asymptomatic ICH was reported in 26 patients (14.7%; 95% CI 9.3-19.7%). Data on expansion of intramural hematoma was not available in 89 patients. One (1%; 95% CI 0.0-6.0%) patient with right vertebral artery dissection treated with IVT experienced hematoma expansion (IPD, unpublished data) although with good recovery (mRS 1 at 3 months). Pseudo-aneurysm was reported in 8 of 133 patients (6.0%; 95% CI 2.6-11.5%) of which this information was available. One asymptomatic subarachnoid bleeding (IPD, no published data) but no symptomatic subarachnoid bleeding was reported. Eight of 176 patients (4.5%; 95% CI 2.3-8.7%) had recurrent stroke. Progression of the infarct was reported in 13 of 161 patients (8.1%; 95% CI 4.4-13.4%) (Table 3a and 3b).

*Functional Outcome*

Functional outcome was available for 158 patients. In 15 cases, mRS could be deducted reliably from the description of the functional status. In total, 41.0% (95% CI 31.4-51.4%) made an excellent recovery (mRS 0-1), whereas 59.5% (95% CI 52.1-66.6%) attained favourable outcome (mRS 0-2) at a median follow-up duration of 3 months (range 5 days – 18 months).

*Regression models*

Predictors of excellent (mRS 0-1) and of favourable (mRS 0-2) functional outcome are presented in Table 4. In the univariate analyses, only stroke severity (NIHSS on admission) was significantly associated with both excellent and favourable outcome. The odds ratio (OR) for excellent outcome was 0.88 (95% CI 0.82-0.93); for each point increase on NIHSS. For favourable outcome this OR was 0.87 (95% CI 0.82-0.92). Regarding location, vertebral artery dissection was significantly associated with excellent outcome compared to carotid artery dissection (OR 2.64, 95% CI 1.24-5.62), but not with favourable outcome. Gender,

age, and trauma were not associated with outcome. Onset-to-treatment-time (OTT) was neither associated with outcome, analyzed as either a continuous or categorical variable. In the multivariate model, we adjusted for stroke severity only, since NIHSS was significantly associated with both excellent and favourable outcome. In this model, the relation between location of the dissected artery (carotid or vertebral artery) and excellent outcome remained significant (OR 3.94, 95% CI 1.40-11.12). After adjustment for stroke severity, combined treatment showed a trend towards favourable outcome compared to IVT alone (OR 3.87, 95% CI 0.93-16.06, p=0.06).

*Publication bias*

Leaving out the results of the case reports did not alter the main findings, suggesting that publication bias did not play a role in case reports compared to the results of the larger studies.

## Discussion

This meta-analysis on IPD presents the largest number of CAD patients treated with thrombolysis to date and suggests that thrombolysis in acute ischemic stroke due to CAD is safe.

Mortality in our study is 8.1% (6.7% in IVT patients), which is comparable with previously published mortality rates in patients with stroke from all causes, treated with thrombolysis. In Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), comprising the largest thrombolysis registry of 6,483 IVT treated patients with stroke from all causes, unadjusted mortality was 11.3%.[50] Patients in our study were more than 20 years younger compared to the population in SITS-MOST, but had more severe symptoms (median NIHSS of 16, versus 12 in SITS-MOST). SICH rate in our study was 3.1% in all patients and 3.3% in patients treated with IVT only. Since SICH was not uniformly defined, we used a pragmatic instead of a fixed definition of SICH. By considering every intracerebral hematoma which was reported as symptomatic by the author, we have a warranted that all clinically relevant SICH are included in our analysis. This heterogeneous definition of SICH makes direct comparison with SICH rates with other studies difficult. In SITS-MOST, according to the broadest definition of SICH (i.e. any deterioration in NIHSS score within 7 days and intracerebral hemorrhage of any type in any post-treatment imaging scan after the start of thrombolytic treatment), the SICH rate was 7.3%.[50] According to a less strict definition of SICH, i.e. clinical deterioration of ≥ 4 points of the NIHSS with parenchymal hematoma type II being the predominant cause of deterioration, this rate was 1.7%. Our rate with mixed definitions of ICH falls precisely in between the outer borders of SITS-MOST. Mortality and functional outcome rates of our study and of SITS-MOST are listed in Table 5.

Favourable outcome in CAD patients in our study was 60% (61% for patients treated with IVT only). Despite the high stroke severity at baseline in our population, the rate of

favourable outcome is somewhat higher than the 55% reported in SITS-MOST. This can be explained by the relatively young age of our study population, with SICH and death rates that are comparable to those observed in SITS-MOST.

In addition to analysis of the primary aims, this study allowed us to indirectly compare the effect of different treatment strategies in the acute phase (IVT only, IAT only or combined procedures) in CAD-related stroke. Studies directly comparing different treatment strategies are not available in literature to data. Adjusted for stroke severity, the combined treatment of chemical lysis and endovascular procedures showed a trend towards favourable outcome. This trend could not be confirmed for excellent outcome, which might be due to the low number of patients receiving this combination of treatments in the acute phase. Therefore, this finding needs to be interpreted with caution. For patients treated with IAT only, there was no association with favourable or excellent outcome. One series compared IVT in 4 patients with endovascular procedures in 6 patients with carotid dissection and tandem occlusion.[23] Patients treated with IVT had worse outcome. However, another series of 18 patients with carotid dissection and tandem occlusion (14 patients treated with IVT only, 4 endovascular procedures) could not confirm these results.[17] Although randomised trials comparing different thrombolytic treatment options in CAD are lacking, our data support the use of IVT as primary therapeutic strategy in stroke patients, regardless of a suspicion of underlying CAD. Since tests to diagnose dissections in the acute phase, such as CTA or MRA, may delay start of IVT in the acute phase of stroke, these should preferably be postponed until emergency treatment has started. IAT or other endovascular procedures should probably be reserved for patients who are not eligible for IVT or who do not recover after IVT.

The most important limitation in this meta-analysis is that no randomized trials were available. The pooled estimates are based on retrospective - and mostly uncontrolled - series and case reports only. Therefore, the results might be influenced by referral bias. Based on

the available data, it seems unlikely that randomized, placebo-controlled trials will be done in the future to investigate the safety and efficacy of thrombolysis in patients with ischemic stroke secondary to a dissection. Data from completed and ongoing thrombolysis studies and larger registries with subgroup analysis based on underlying aetiology are needed for direct comparisons between groups.

Another limitation is that we applied a wide treatment window of 24 hours after symptom onset, which is beyond the current guidelines of 4.5 hours for IVT. We defined a longer time-window to allow inclusion of IVT plus IAT studies as well, as long as they were started in the acute phase of stroke and not because of deterioration one or more days after onset of symptoms. We consider the latter a different group of patients. Median treatment time in our study was 165 minutes after symptom onset, indicating that thrombolytic therapy was mostly administered in the very acute phase of the stroke, which was the focus of our study.

In conclusion, thrombolysis seems to be safe in acute ischemic stroke due to CAD. Mortality and SICH rate as well as outcome after thrombolysis in this subgroup are comparable with the rates in stroke patients from all causes treated with thrombolysis.. In our opinion, thrombolytic therapy should therefore not be withheld in patients with CAD related ischemic stroke.

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**Table 1.** Characteristics of included series (case-reports are not listed).

| **Study** | **Design** | **Population** | **No. of patients included in meta-analysis** | **Treatment** |
|---|---|---|---|---|
| Engelter et al. (2010) [11] | retrospective, multicenter multicentre | 55 consecutive patients with stroke due to cervical artery dissection treated with IVT | 55 | IVT |
| Vergouwen et al. (2009)[26] | retrospective, single centre | 8 consecutive patients with stroke due to extracranial artery dissection | 6 | IVT, IAT |
| Putaala et al. (2009)[24] | retrospective, single centre | 48 consecutive patients with stroke aged 16-49 treated with IVT | 12 | IVT |
| Huang et al. (2009)[22] | retrospective, single centre | 73 patients with cervicocranial arterial dissection | 1 | IAT |
| Cerrato et al. (2008)[19] | retrospective, single centre | 3 patients with vertebral artery dissection and basilar artery occlusion treated with IAT | 3 | IAT. |
| Baumgartner et al. (2008)[17] | retrospective, single centre | 18 consecutive patients with internal carotid artery dissection and a symptomatic middle cerebral artery occlusion | 18 | IVT, combined |
| Lavallée et al. (2007)[23] | retrospective, single centre | 10 patients with tandem internal carotid and middle cerebral artery occlusion with internal carotid dissection | 5 | IVT, combined |
| Dabitz et al. (2007)[20] | retrospective, single centre | 10 consecutive patients with acute cerebral ischemia associated with proximal carotid artery occlusion | 3 | combined |

| **Study** | **Design** | **Population** | **No. of patients included in meta-analysis** | **Treatment** |
|---|---|---|---|---|
| Georgiadis et al. (2005)[27] | retrospective, multicentre | 33 consecutive patients with stroke due to spontaneous carotid dissection treated with IVT | 33 | IVT |
| Arnold et al. (2002)[16] | retrospective, single centre | 9 patients with cervical artery dissection treated with thrombolysis | 9 | IVT, IAT |
| Bin Saeed et al. (2000)[18] | retrospective, single centre | 26 patients with vertebral artery dissection | 2 | IAT |
| Derex et al. (2000)[21] | retrospective, single centre | 11 consecutive patients with acute ischemic stroke related to internal carotid artery dissection treated with IVT | 11 | IVT |
| Ahmad et al. (1999)[15] | retrospective, multicentre | 18 patients with cervicocerebral artery dissections | 2 | IAT |
| Rudolf et al. (1999)[25] | retrospective, single centre | 15 consecutive patients with internal carotid artery occlusion treated with IVT | 6 | IVT |

IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis; SAH = subarachnoid hemorrhage; SICH = symptomatic intracerebral hemorrhage; AICH = asymptomatic intracerebral hemorrhage; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Score, FIM= Functional Independence Measure; BI = Barthel Index

**Table 2.** Baseline characteristics of all included CAD patients: individual patient data (IPD)

| **Baseline characteristics** | **IPD** |
|---|---|
| Patients, n | 180 |
| Men, n (%) | 57 (32) |
| Mean age, years ± SD | 46 ± 11 |
| Preceding trauma, n (%) | 31 (17) |
| Stroke severity | |
| presenting mean NIHSS ± SD (range) | 15.8 ± 6.9 (1-36) |
| median NIHSS (IQR) | 16 (11-20) |
| *mild stroke (NIHSS 1-7), n (%)* | *21 (15)* |
| *moderate stroke (NIHSS 8-14), n (%)* | *42 (25)* |
| *severe stroke (NIHSS ≥ 15), n (%)* | *86 (60)* |
| Location of dissection | |
| carotid artery, n (%) | 131 (73) |
| *left carotid artery (%)* | *66 (50)* |
| *right carotid artery (%)* | *56 (43)* |
| *bilateral carotid artery (%)* | *4 (3)* |
| *unknown* | *5 (4)* |
| vertebral artery, n (%) | 48 (27) |
| both, n (%) | 1 (1) |
| Occlusion before treatment, n (%) | 107 (83) |
| Intracranial extension, n (%) | 16 (10) |
| Mean onset to treatment time ± SD (minutes) | 195 ± 123 |
| Median (IQR) | 165 (125-225) |
| Treatment | |
| IVT only, n (%) | 121 (68) |
| IAT only, n (%) | 36 (20) |
| combined, n (%) | 22 (12) |
| Mean duration of follow-up ± SD (months) | 3.7 (2.4) |

SD = standard deviation; NIHSS = National Institutes of Health Stroke Scale; IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis; IQR = interquartile range

**Table 3a**. Safety and outcome in CAD treated with thrombolytic therapy

| **Event** | **Proportion** | **Crude estimates** | **Adjusted for heterogeneity** |
|---|---|---|---|
| | | % (95% CI) | % (95% CI) |
| Mortality | 14/173 | 8.1 (4.8 - 13.1) | 8.1 (4.9 - 13.2) |
| SICH | 8/180 | 4.4 (2.1 - 8.7) | 3.1 (1.3 - 7.2) |
| Recurrent stroke | 8/177 | 4.5 (2.2 - 8.8) | 4.5 (2.3 - 8.7) |
| mRS 0-1 | 63/173 | 36.4 (29.6 - 43.8) | 41.0 (31.4 - 51.4) |
| mRS 0-2 | 103/173 | 59.5 (52.1 - 66.6) | 59.5 (52.1 - 66.6) |

SICH = symptomatic intracerebral hemorrhage; mRS = modified Rankin Score

**Table 3b.** Adverse events and outcome in CAD-patients treated with IVT only

| Event | Proportion | Crude estimates | Adjusted for heterogeneity |
|---|---|---|---|
| | | % (95% CI) | % (95% CI) |
| Death | 8/120 | 6.7 (2.2 - 11.1) | 6.7 (3.4 -13.8) |
| SICH | 4/121 | 3.3 (1.0 - 8.5) | 3.3 (1.2 - 8.5) |
| Recurrent stroke | 8/118 | 6.8 (3.3 - 13.0) | 4.5 (3.4 -13.0) |
| mRS 0-1 | 40/120 | 33.3 (25.5 - 42.2) | 41.0 (25.5 - 42.2) |
| mRS 0-2 | 73/120 | 60.8 (51.9 - 69.1) | 59.5 (51.8 - 69.1) |

SICH = symptomatic intracerebral hemorrhage; mRS = modified Rankin Score

**Table 4**. Univariate and multivariate analysis. Odds for excellent and favourable outcome, multivariate analysis is adjusted for stroke severity by means of the NIHSS before start of treatment.

| | **mRS 0 - 1** | | | | **mRS 0 - 2** | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Adjusted for stroke severity | | Univariate | | Adjusted for stroke severity | |
| Variables | OR (95% CI) | p | OR (95% CI) | p | OR (95%CI) | p | OR (95%CI) | p |
| Gender [female] | 0.73 (0.37-1.43) | 0.35 | 0.51 (0.22-1.15) | 0.11 | 1.19 (0.62-2.29) | 0.59 | 0.92 (0.43-1.96) | 0.83 |
| Age | 1.01 (0.98-1.04) | 0.91 | 1.00 (0.96-1.04) | 0.99 | 1.00 (0.98-1.03) | 0.77 | 1.00 (0.97-1.03) | 0.97 |
| Preceding trauma | 1.79 (0.67-4.77) | 0.24 | 0.43 (0.09-2.03) | 0.29 | 1.70 (0.62-4.66) | 0.30 | 0.82 (0.21-3.20) | 0.78 |
| Dissected artery [vertebral artery] | 2.64 (1.24-5.62) | 0.01* | 3.94 (1.40-11.12) | 0.01* | 1.11 (0.54-2.28) | 0.78 | 1.92 (0.72-5.11) | 0.19 |
| Onset to treatment time | | | | | | | | |
| continuous | 1.00 (1.00-1.00) | 0.72 | 1.00 (0.99-1.00) | 0.42 | 1.00 (1.00-1.00) | 0.16 | 1.00 (0.99-1.00) | 0.15 |
| < 120 minutes | reference | | | | | | | |
| 120-180 minutes | 0.75 (0.36-1.57) | 0.44 | 0.74 (0.32-1.71) | 0.47 | 0.68 (0.34-1.34) | 0.26 | 0.75 (0.36-1.59) | 0.46 |
| >180 minutes | 0.63 (0.15-2.58) | 0.52 | 0.27 (0.03-2.83) | 0.27 | 0.32 (0.09-1.18) | 0.09 | 0.22 (0.03-1.52) | 0.13 |
| NIHSS | 0.88 (0.82-0.93) | 0.00* | --- | --- | 0.87 (0.82-0.92) | 0.00* | --- | --- |
| Treatment | | | | | | | | |
| IVT only | reference | | | | | | | |
| IAT only | 1.49 (0.63-3.55) | 0.36 | 2.82 (0.83-9.63) | 0.10 | 0.50 (0.23-1.10) | 0.09 | 0.84 (0.30-2.38) | 0.75 |
| combined | 1.93 (0.71-5.28) | 0.22 | 1.83 (0.45-7.46) | 0.40 | 2.58 (0.81-8.18) | 0.11 | 3.87 (0.93-16.06) | 0.06 |

* $p < 0.05$. mRS = modified Rankin Score; OR = odds ratio; CI = confidence interval; NIHSS = National Institutes of Health Stroke Scale; IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis

**Table 5.** Comparison of the safety of thrombolysis in patients with CAD-related stroke (current meta-analysis) compared with patients with stroke from all causes treated with IV thrombolysis (data from SITS-MOST). [50]

| | **CAD patients** | | **Stroke from all causes** |
|---|---|---|---|
| | All patients (n = 180) | IVT only (n = 121) | SITS-MOST (n = 6.483) |
| | % (95% CI) | % (95% CI) | % (95 CI) |
| Mortality | 8.1 (4.9 - 13.2) | 6.7 (3.4 - 12.8) | 11.3 (10.5 -12.1) |
| SICH | 3.1 (1.3 - 7.2) | 3.3 (1.2 - 8.5) | 1.7 - 7.3* |

***** Range of SICH rates in SITS-MOST, depending on the definition.

**Contributors**

SMZ, MDIV and PJN designed the study, SMZ and PJN did the data search and extracted data, SMZ, NvG and PJN did the statistical analysis. SMZ, NvG and PJN designed the tables. All authors contributed to the writing of the Article.

**Conflicts of interest**

We have no conflicts of interest.

**Appendix**. Overview of centres providing IPD

Individual patient data of case series were provided by the following centres:
University Hospital Lausanne (Swiss): 27 patients (22 IVT, 5 combined treatment); University Hospital Bern (Swiss): 25 patients (9 IVT, 13 IAT, 3 combined treatment); University Hospital Zurich (Swiss): 24 patients (21 IVT, 3 IAT); University Hospital Basel (Swiss): 22 patients (20 IVT, 2 IAT); University Hospital Helsinki (Finland): 12 patients (12 IVT); University Hospital in Mannheim (Germany): 7 patients (7 IVT); Academic Medical Centre University of Amsterdam (Holland): 6 patients. Other authors provided additional information regarding clinical status [20;21;37] or treatment.[23]